Brainstem Serotonergic Deficiency in Sudden Infant Death Syndrome

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~ February 11, 2010 ~

SIDS is defined as the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history.[1] Our current working "triple-risk" hypothesis posits that SIDS results from the simultaneous occurrence of an underlying vulnerability in the infant, a critical developmental period during infancy, and exposure of an infant to an exogenous stressor.[2] An underlying vulnerability is a pathologic abnormality that it in itself is not necessarily fatal, but when interacting with other factors can act as the tipping point leading to a lethal event. In the case of SIDS, the critical developmental period is the first half of infancy when physiologic and anatomic growth and development are very rapid and thus inherently unstable, especially during sleep. Exogenous stressors are risk factors for SIDS, especially those that pose a risk of asphyxia to the sleeping infant. Prone sleep position, sleeping on a soft surface, having the head covered, and/or exposure to cigarette smoke are particularly important risk factors. Exogenous risk factors have been identified and confirmed through numerous epidemiologic studies of large numbers of infants.

Our team of investigators, led by Dr. Hannah Kinney, has been pursuing for many years what makes an infant vulnerable to SIDS by concentrating on the medullary serotonergic system. This system plays a crucial role in the control and homeostasis of the respiratory, cardiovascular, and autonomic systems.

Our recent report that brainstem serotonin (5-HT) and tryptophan hydroxylase (TPH2) levels were lower in SIDS cases than in age-adjusted controls provides further evidence that defects in the medullary serotonergic system are important in SIDS.[3] 5-HT and TPH2 levels critical to respiration were 26% and 22% lower, respectively, in brainstems from SIDS cases compared to controls. This finding indicates that 5-HT levels were low as a result of decreased synthesis rather than increased degradation. Serotonin receptor (5-HT_{1A}) binding was also reduced, thus confirming earlier observations.

How do our reported abnormalities in the serotonin metabolism relate to our "triple risk" hypothesis for SIDS? Remember that the typical case of SIDS usually involves an apparently healthy infant between one and six months of age who has been sleeping and is later discovered lifeless. Even though one or more of the above-mentioned SIDS risk factors that threatens the sleeping infant with asphyxia, hypercarbia, and/or hypoxia are usually present, evaluation of both the circumstances of death after death scene investigation as well as the postmortem examination does not reveal a definitive cause of death. Therefore, the diagnosis defaults to SIDS. In this scenario, the developmental period and the exogenous SIDS risk factors are present, but according to our hypothesis, infant vulnerability must also be present for death to occur. We have found that a high percentage of infants we studied have abnormalities in the medullary serotonergic system that unmasks or exposes the danger posed by the combination of sleep during the critical developmental period while sleeping in a potentially asphyxial environment. Thus, when medullary serotonergic system abnormalities are present, the infant may not be able to rescue itself from an asphyxial environment, i.e., compared to an infant without these abnormalities, an affected infant may not raise or turn its head to remove its nose and mouth from a face down position on a soft sleep surface.

Much work remains to be done to expand our understanding of the interaction of infant development, exogenous risk factors, and the medullary serotonergic system. But it is hoped through this understanding that it will be possible to predict which infants are at risk of SIDS and thereby intervene somehow before death occurs. This is several years away, however.

This work was undertaken by investigators from Harvard, UCSD/Rady Children's Hospital-San Diego (Dr. Henry Krous, Elisabeth Haas), the San Diego Medical Examiner's Office (Dr. Christina Stanley), University of New England College of Osteopathic Medicine, Dartmouth, and the New England Research Institutes. The study cases were obtained from the San Diego SIDS/SUDC Research Project after undergoing postmortem examination at the San Diego Medical Examiner's Office and Children's Hospital Boston. This work could not have been carried out without California law and the generous support of many parent and family survivors of infants dying of SIDS.

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2. Kinney HC, Richerson GB, Dymecki SM, Darnall RA, Nattie EE. The brainstem and serotonin in the sudden infant death syndrome. *Annu Rev Pathol.* 2009; 4:517-550.
3. Duncan JR, Paterson DS, Hoffman JM, et al. Brainstem serotonergic deficiency in sudden infant death syndrome. *JAMA.* 2010; 303:430-437. *

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** Note: For a complete copy of the February 3, 2010 Journal of the American Medical Association article go to*
http://www.firstcandle.org/cms/wp-content/uploads/2010/02/Feb._3_-_Brainstem_Serotonergic_Deficiency_in_SIDS-JAMA.pdf

Distributed by the California SIDS Program under funding by the California Department of Public Health, Maternal, Child and Adolescent Health Division

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